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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/586,056	06/11/2007	Elimelech Rochlin	27526U	2440

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NATH & ASSOCIATES
112 South West Street
Alexandria, VA 22314

EXAMINER	
NWAONICHA, CHUKWUMA O	
ART UNIT	PAPER NUMBER
1621	

MAIL DATE	DELIVERY MODE
03/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/586,056	ROCHLIN ET AL.	
	Examiner	Art Unit	
	CHUKWUMA O. NWAONICHA	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 06 February 2008.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 57-104 is/are pending in the application.

4a) Of the above claim(s) 79-104 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 57,58,60-63,66,70-75,77 and 78 is/are rejected.

7)☒ Claim(s) 59,64,65,67-69 and 76 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Current Status

1. This action is responsive to Applicants' amendment of 6 February 2008.

2. Claims 57-104 are pending in the application.

Election/Restrictions

Applicant's election without traverse of Group 1 (claims 57-78) in the reply filed on 6 February 2008 is acknowledged. Applicants are reminded of their right to file divisional applications to the non-elected claims. Claims 79-104 are withdrawn from further consideration.

Applicants' are reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

Applicants' claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 57, 66, 71-75, 77 and 78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 57, 66, 71-75, 77 and 78 are rejected because the claims recite "R^2 represents a hydrophobic group, Z represents a protecting group and X represents a leaving group", which are not properly defined in the specification. The metes and bounds of the claims are unclear. Correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

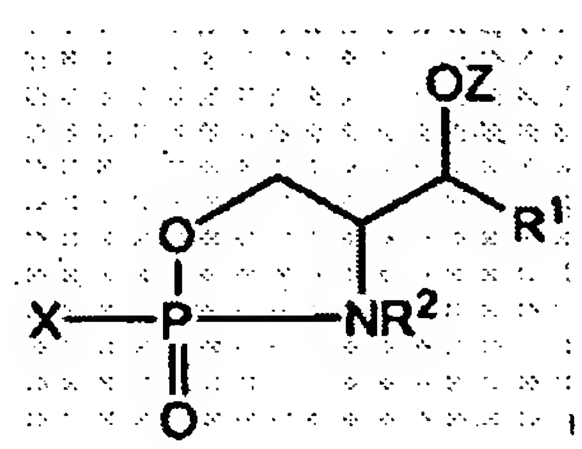
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 57, 58, 60-63, 66, 70-75, 77 and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deigner et al., {Synthesis of [^{32}P] labelled 1-O-alkyl-2-desoxy-2-amino-*SN*-glycero-3-phosphocholines, JOURNAL OF LABELLED COMPOUNDS

AND RADIOPHARMCEUTICALS, vol. 34, no. 2, 1994, pages 185-190}, Deigner et al., (2) {Rapid synthesis of 2-desoxy-2-amino-3-phosphocholine-glycerinic-acid-alkylester, 1-alkyl-l-desoxy- and 1-o-alkyl-2-desoxy-2-amino-sn-glycero-3-phosphocholines,-3-phospho-N,N'-dimethylethanolamine and-3-phospho-Fmoc-serine-methylester, CHEMISTRY AND PHYSICS OF LIPIDS, vol. 61, 1992, pages 199-208}, or Lorene et al., {Synthesis of N-Lost derivatives. II. Reaction of N,N-bis(2-chloroethyl) phosphoramidic dichloride with 1-aminopropane-2,3-diol, ARCHIV DER PHARMAZIE (WEINHEIM, GERMANY) , 319(11), 1023-7, 1986}.

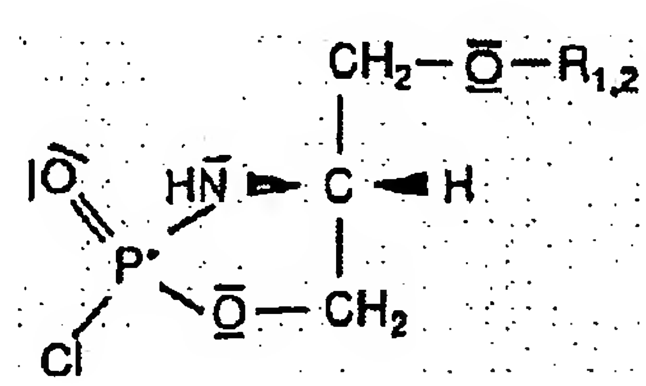
Applicants claim an oxazaphospholane compound of the general formula 1; wherein all the variables are as defined in the claims.



formula 1

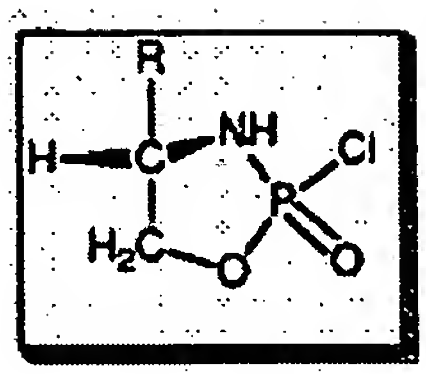
Determination of the scope and content of the prior art (M.P.E.P. §2141.01)

Deigner et al. teach a compound of the formula 2. See page 186.



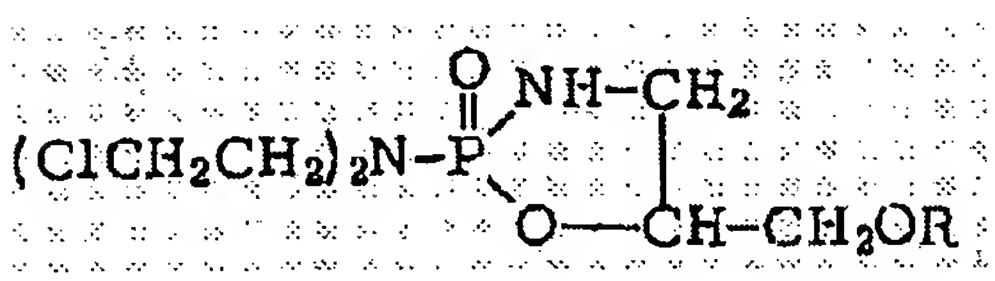
formula 2

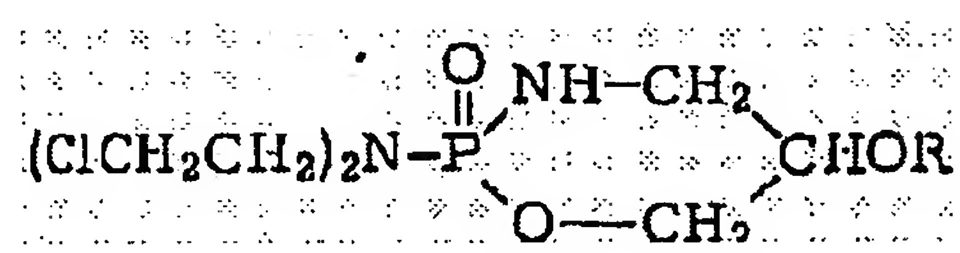
Deigner et al. (2) teach a compound of the formula 3. See page 200.



formula 3

Lorene et al. teach the compounds of the formula 4. See page 1025.





formula 4

<u>Ascertainment of the difference between the prior art and the claims (M.P.E.P.. §2141.02)</u>

Applicants claimed the oxazaphospholane compound of the general formula 1 differs from the teaching of the prior art references in that the instantly claimed compound of the general formula 1 is a homolog of the prior arts compounds.

<u>Finding of prima facie obviousness--rational and motivation (M.P.E.P.. §2142-2143)</u>

The instantly claimed oxazaphospholane compounds of the general formula 1 would have been suggested to one of ordinary skill because one of ordinary skill wishing to obtain the oxazaphospholane compounds of the general formula 1 is taught to select the compounds of Deigner et al., Deigner et al. (2) or Lorene et al.

One of ordinary skill in the art would have a reasonable expectation of success in practicing the instant invention by varying the substituents on the oxazaphospholane ring to arrive at the instantly claimed oxazaphospholane compounds. Said person

would have been motivated to practice the teaching of the reference cited because of the physicochemical and biological properties of oxazaphospholane compounds. Additionally, the prior arts compounds are homologs of the claimed compounds of the general formula 1, and homologs are obvious. The instantly claimed invention would therefore have been obvious to one of ordinary skill in the art.

Allowable Subject Matter

Claims 59, 64, 65, 67-69 and 76 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chukwuma O. Nwaonicha whose telephone number is 571-272-2908. The examiner can normally be reached on Monday thru Friday, 8:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne (Bonnie) Eyler can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/YVONNE L. EYLER/
Supervisory Patent Examiner, Art Unit 1621
/Chukwuma O. Nwaonicha/
Examiner, Art Unit 1621

Notice of References Cited	Application/Control No. 10/586,056	Applicant(s)/Patent Under Reexamination ROCHLIN ET AL.	
	Examiner CHUKWUMA O. NWAONICHA	Art Unit 1621	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Deigner et al., Rapid synthesis of 2-desoxy-2-amino-3-phosphocholine-glycerinic-acid-alkylester, 1-alkyl-l-desoxy- and 1-o-alkyl-2-desoxy-2-amino-sn-glycero-3-phosphocholines,-3-phospho-N,N'-dimethylethanolamine and-3-phospho-Fmoc-serine-methylester, CHEMISTRY AND PHYSICS OF LIPIDS, vol. 61, 1992, pages 199-208
	V	Deigner et al., Synthesis of [32P] labelled 1-O-alkyl-2-desoxy-2-amino-sn-glycero-3-phosphocholines, JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMCEUTICALS, vol. 34, no. 2, 1994, pages 185-190
	W	Lorene et al., Synthesis of N-Lost derivatives. II. Reaction of N,N-bis(2-chloroethyl)phosphoramidic dichloride with 1-aminopropane-2,3-diol, ARCHIV DER PHARMAZIE (WEINHEIM, GERMANY) , 319(11), 1023-7, 1986
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXXIV, No. 2

SYNTHESIS OF [^{32}P] LABELLED 1-O-ALKYL-2-DESOXY-2-AMINO-*SN*-GLYCERO-3-PHOSPHOCHOLINES

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Im Neuenheimer Feld 364, 69120 Heidelberg/Germany

SUMMARY

The syntheses of N-substituted 1-O-alkyl-2-desoxy-2-amino-*sn*-glycero-3-[^{32}P]phosphocholines were performed in four steps starting from [^{32}P] $POCl_3$ and the corresponding 1-O-alkyl-2-amino-propane-3-ols in 5-7 % total yield.

KEY WORDS

[^{32}P]etherphospholipids; 1-O-alkyl-2-desoxy-2-amino-sn-glycero-3-[^{32}P]phosphocholines

INTRODUCTION

Derivatives of 1-O-alkyl-2-desoxy-2-amino-*sn*-glycero-3-phosphocholine are potent inhibitors of phospholipase A_2 [1, 2] and potential ligands of the receptor of the platelet activating factor (PAF). Isotopically labelled, 2-amino-etherphospholipids therefore are of potential value in investigations involving interactions of phospholipids with cellular membranes as well as in metabolic studies.

In this report we describe the preparation of [^{32}P] labelled 2-desoxy-2-amino-*sn*-glycero-ether-phospholipids utilizing [^{32}P] $POCl_3$ to introduce the radioactive label and 4-substituted 2-chloro-2-oxo-1,3,2-oxaza-[^{32}P]phospholanes as versatile intermediates.

RESULTS AND DISCUSSION

The synthetic route to labelled 1-O-alkyl-2-desoxy-2-amino-*sn*-glycero-3-phosphocholines is outlined in the scheme. Preparation of [^{32}P] labelled 2-desoxy-2-amino-lysophospholipids was carried out according to the synthetic sequence for unlabelled 2-amino-phospholipids published by us previously [3].

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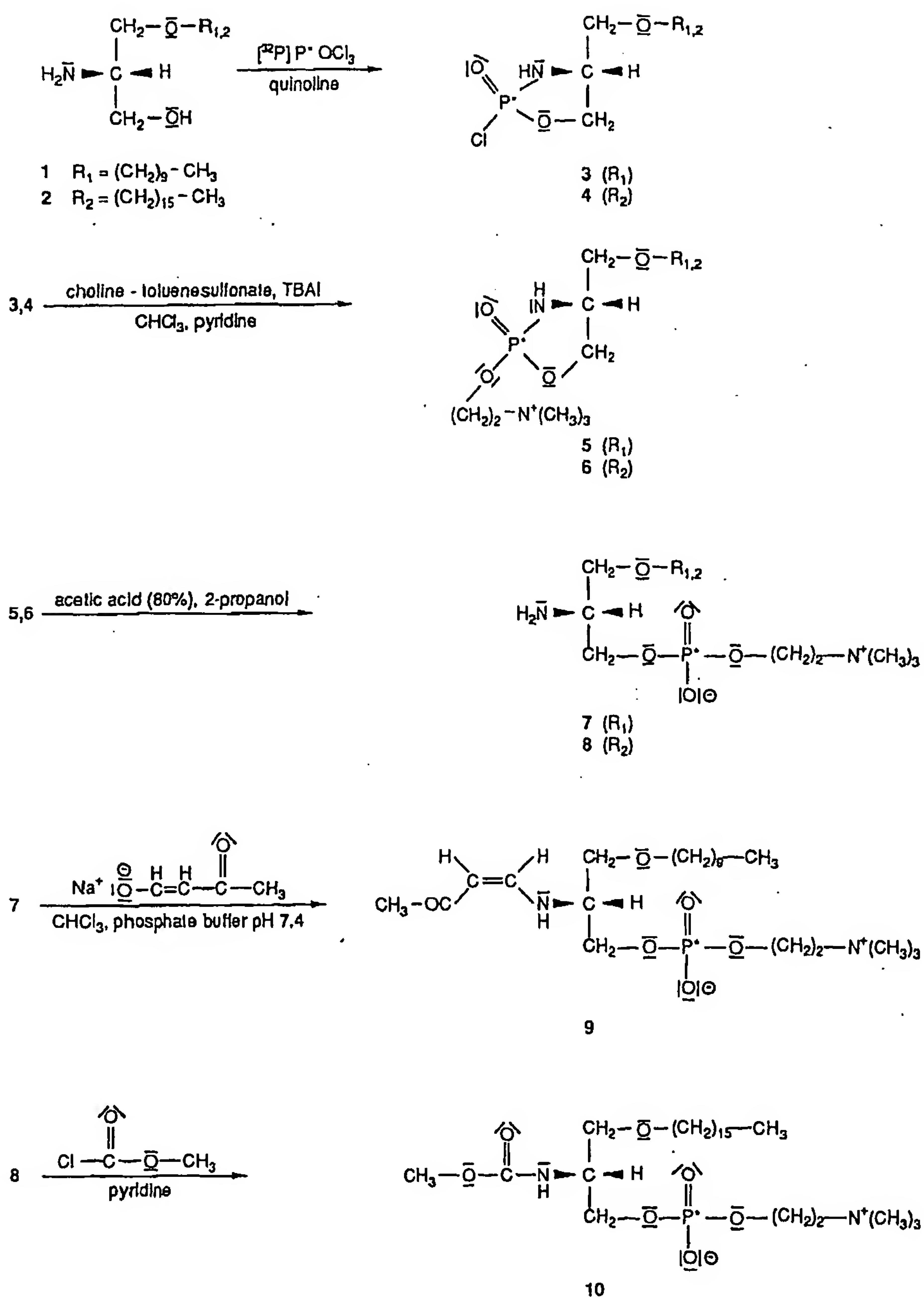
* to whom correspondence should be adressed

0362–4803/94/020185–05$07.50

Received 21 September, 1993
Revised 4 October, 1993



SCHEME

Equilibration of [^{32}P] phosphoric acid with phosphorus oxychloride yielded isotopically labelled $POCl_3$; reaction with the corresponding 1-O-alkyl-2-amino-propane-3-ol (1, 2) gave the labelled oxazaphospholane intermediates (3, 4). The choline group was introduced by nucleophilic exchange of the chlorine, acid

hydrolysis of (5), (6) opened the ring to give the desired 1-O-alkyl-2-desoxy-2-amino-*sn*-glycero-[^{32}P]-phosphocholines (7) and (8). The total yield of the three consecutive steps was lower starting from the long-chain aminoalcohol (2) (12% vs. 32%) suggesting a decreased reactivity along with increasing carbon chain length. Conversion of the 2-amino-lysophospholipids (7) and (8) with the sodium salt of 1-hydroxy-but-1-en-3-on or with methylchloroformate and purification by chromatography on thin layer plates provided the labelled vinylogous amide (9) and the carbamic-acid-methylester (10) with a specific activity of approximately 720 MBq/mmol and a radiochemical purity of 95-96%. The specific radioactivity of the phospholipids was 0.78 of the theoretical value, a result which can be explained by incomplete exchange with [^{32}P]phosphoric acid .

MATERIALS

Tetrabutyl ammonium iodide was purchased from Fluka (Buchs, Switzerland), phosphorus oxychloride and p-toluenesulfonic acid from Aldrich (Steinheim, Germany). Chloroform and methanol were obtained from J. T. Baker (Deventer, Holland) and distilled from P_2O_5 and from Mg prior to use. Silica gel (grade 60, 70-230 mesh) for column chromatography and 2-propanol was from Machery-Nagel (Düren, Germany). TLC plates (0.5 mm, F 254) were from E. Merck (Darmstadt, Germany) and precluted with methanol. [^{32}P]phosphoric acid (314-337 TBq/mmol) was from Du Pont de Nemours Deutschland GmbH (Bad Homburg).

METHODS

Thin-layer chromatography (TLC) and column chromatography were performed using a mixture of chloroform/methanol/water (65:45:8, v/v) as mobile phase. Phospholipids were detected with "Phospray" (Supelco, Bad Homburg, Germany). Mass spectra were obtained using a MAT 311 A mass spectrometer (Varian, Bremen, Germany) equipped with a FAB ion gun (Xe, 6 KV, ion current 1 mA) from Ion Tech (Teddington, U. K.) and glycerol as matrix. ^{1}H-NMR-spectra were recorded at 250 MHz (WM-250, Bruker Physik AG, Karlsruhe, Germany); tetramethyl silane was used as internal reference. Spectra were run in acetonitrile-D_3 or in $CDCl_3$/methanol-D_4, 2:1 (v/v). Multiplicities are reported as singlet (s), doublet (d), triplet (t) or multiplet (m).

[^{32}P] phosphorus oxychloride

Labelled phosphorus oxychloride was obtained applying the method of Keenan et al. [4].
[^{32}P] phosphoric acid (370 MBq, 314-337 TBq/mmol) was mixed with freshly distilled phosphorus oxychloride (30 μl, 0.32 mmol) to give a theoretical specific activity of 1.12 GBq/mmol (calculated for 100% conversion to $POCl_3$) and stirred for 24 h at 107°C in a screwed vial.

1-O-decyl-2-desoxy-2-amino-*sn*-glycero-[^{32}P]phosphocholine (7) and 1-O-hexadecyl-2-desoxy-2-amino-*sn*-glycero-3-[^{32}P]phosphocholine (8)

To 12 μl (129 μmol) of [^{32}P] phosphorus oxychloride dissolved in chloroform, a solution of 30 mg (130 μmol) of 1-O-decyl-2-amino-propane-3-ol (1) or 41 mg (130 μmol) 1-O-hexadecyl-2-amino-propane-3-ol (2) and 35 μl (290 μmol) quinoline was added dropwise at 4°C. The mixture was allowed to warm up at room temperature, then stirred at 55°C for 16 h.

The resulting solution of 1-O-decyl-2,3-(2'chloro-2'oxo-1',3',2')-oxaza[^{32}P]phospholane (3) or 1-O-hexadecyl-2,3-(2'chloro-2'oxo-1',3',2')-oxaza[^{32}P]phospholane (4) was cooled to 12°C and 55mg (0.2 mmol) choline tosylate in 0.3 ml pyridine was added. After stirring for 24 h at 55°C, the solvents were removed *in vacuo*, and the residue containing the crude oxazaphospholanes (5) or (6) was redissolved in 1 ml of 2-propanol/acetic acid (80%) 3:2 (v/v). Hydrolysis was carried out by stirring at 50°C for 30 min and at room temperature for additional 2 h. The solvents were removed by distillation *in vacuo* at under 40°C and silica gel chromatography afforded 16.3 mg (41 μmol, 31%) of (7) and 7.2 mg (15 μmol, 12%) of (8); MS (FAB; glycerol; pos. mode): m/z =397 [M+H]$^+$ (7) and m/z =481 [M+H]$^+$ (8).

1-O-decyl-2-desoxy-2-(1'-amino-but-1'-en-3'-on)-*sn*-glycero-3-phosphocholine (9)

To 16.3 mg (41 μmol) of (7), dissolved in 2 ml of a biphasic mixture (1:1, v/v) of chloroform/phosphate buffer (20 mM, pH 7.4) 200 mg (1.85 mmol) of the sodium salt of 1-hydroxy-but-1-en-3-on [5] were added and the solution stirred for 24 h at room temperature. The solvents were removed by distillation *in vacuo* and the residue purified by thin layer chromatography yielding 2.8 mg (6 μmol, 15%) of (9) (cis configuration, specific activity 724 MBq/mmol)

MS (FAB; glycerol; pos. mode): m/z = 465 [M+H]$^+$

^{1}H-NMR ($CDCl_3$/D_4-methanol, 2:1) δ ppm:

6.8 (1H, d, -C$\underline{H}$=CH-C=O), 4.95 (1H, d, -CH=C$\underline{H}$-C=O), 4.2 (1H, m, *sn*-2-C$\underline{H}$), 3.95 (2H, m, C$\underline{H}_2$-CH_2-$N^+(CH_3)_3$), 3.9-3.8 (2H, t, *sn*-3-C$\underline{H}_2$), 3.6 (2H, m, -C$\underline{H}_2$-$N^+(CH_3)_3$), 3.45 (2H, m, *sn*-1-C$\underline{H}_2$-), 3.3 (3H, s, O=C-C$\underline{H}_3$), 3.2 (9H, s, -N^+(C$\underline{H}_3$)$_3$), 1.5 (2H, m, -C$\underline{H}_2$-$(CH_2)_8$-CH_3), 1.25 (16H, m, -CH_2-(C$\underline{H}_2$)$_8$-CH_3), 0.85 (3H, t, -$(CH_2)_9$-C$\underline{H}_3$).

1-O-hexadecyl-2-desoxy-2-amino-carbamic-acid-methylester-*sn*-glycero-3-phosphocholine (10)

To a solution of 7.2 mg (15 μmol) (8) in chloroform/pyridine (3 ml, 5:1), 10 μl (130 μmol) of methylchloroformate were added dropwise at 0°C; the reaction mixture was allowed to warm up to room temperature and stirred for another 4 h. Evaporation *in vacuo* afforded crude (10) which was subjected to thin layer chromatography to give 4.8 mg (9 μmol, 60%) of (10) (specific activity 715 MBq/mmol)

MS (FAB; glycerol; pos. mode): m/z = 523 [M+H]$^+$.

^{1}H-NMR (CD_3-C≡N) δ ppm:

4.2 (1H, m, *sn*-2-C$\underline{H}$), 3.9 (2H, m, C$\underline{H}_2$-CH_2-$N^+(CH_3)_3$, 3.9-3.8 (2H, m, *sn*-3-C$\underline{H}_2$), 3.6 (3H, s, -O-C$\underline{H}_3$), 3.55 (2H, m, -C$\underline{H}_2$-$N^+(CH_3)_3$, 3.45 (2H, m, *sn*-1-C$\underline{H}_2$-), 3.2 (9H, s, -N^+C$\underline{H}_3$)$_3$, 1.5 (2H, m, -C$\underline{H}_2$-$(CH_2)_{14}$-CH_3), 1.25 (28H, m, -CH_2-(C$\underline{H}_2$)$_{14}$-CH_3), 0.85 (3H, t, -$(CH_2)_{15}$-C$\underline{H}_3$).

ACKNOWLEDGEMENT

The authors are indebted to Professor R. Neidlein, Pharmazeutisch-Chemisches Institut Heidelberg, for continous support. Support of this work by the Deutsche Forschungsgemeinschaft (DFG) is gratefully acknowledged.

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[Ph 155]

Arch. Pharm. (Weinheim) *319*, 1023–1027 (1986)

Synthesen von N-Lost-Derivaten, 2. Mitt.[1)]

Reaktion von N-Bis(2-Chlorethyl)phosphorsäureamid-dichlorid mit 1-Aminopropan-2,3-diol

Peter Lorenz und Manfred Wiessler*

Institut für Toxikologie und Chemotherapie, Deutsches Krebsforschungszentrum,
Im Neuenheimer Feld 280, 6900 Heidelberg
Eingegangen am 24. Oktober 1985

Die Umsetzung des Phosphamidichlorides **1** mit 1-Aminopropan-2,3-diol **(3)** liefert nicht das gewünschte 5-Hydroxy-cyclophosphamid **8** sondern die isomere 5-Ring-Verbindung **9**. Die Strukturzuordnung wird durch unabhängige Synthese von **9** über den Benzylether **14** gesichert.

Synthesis of N-Lost Derivatives, II[1)]: Reaction of N,N-bis(2-Chloroethyl)phosphoramidic dichloride with 1-Aminopropane-2,3-diol

The reaction between the phosphoramidic dichloride **1** and 1-aminopropane-2,3-diol **(3)** affords the five membered ring **9** and not the desired 5-hydroxycyclophosphamide **8**. The structural assignment was based on an independent synthesis of **9** *via* the benzyl ether **14**.

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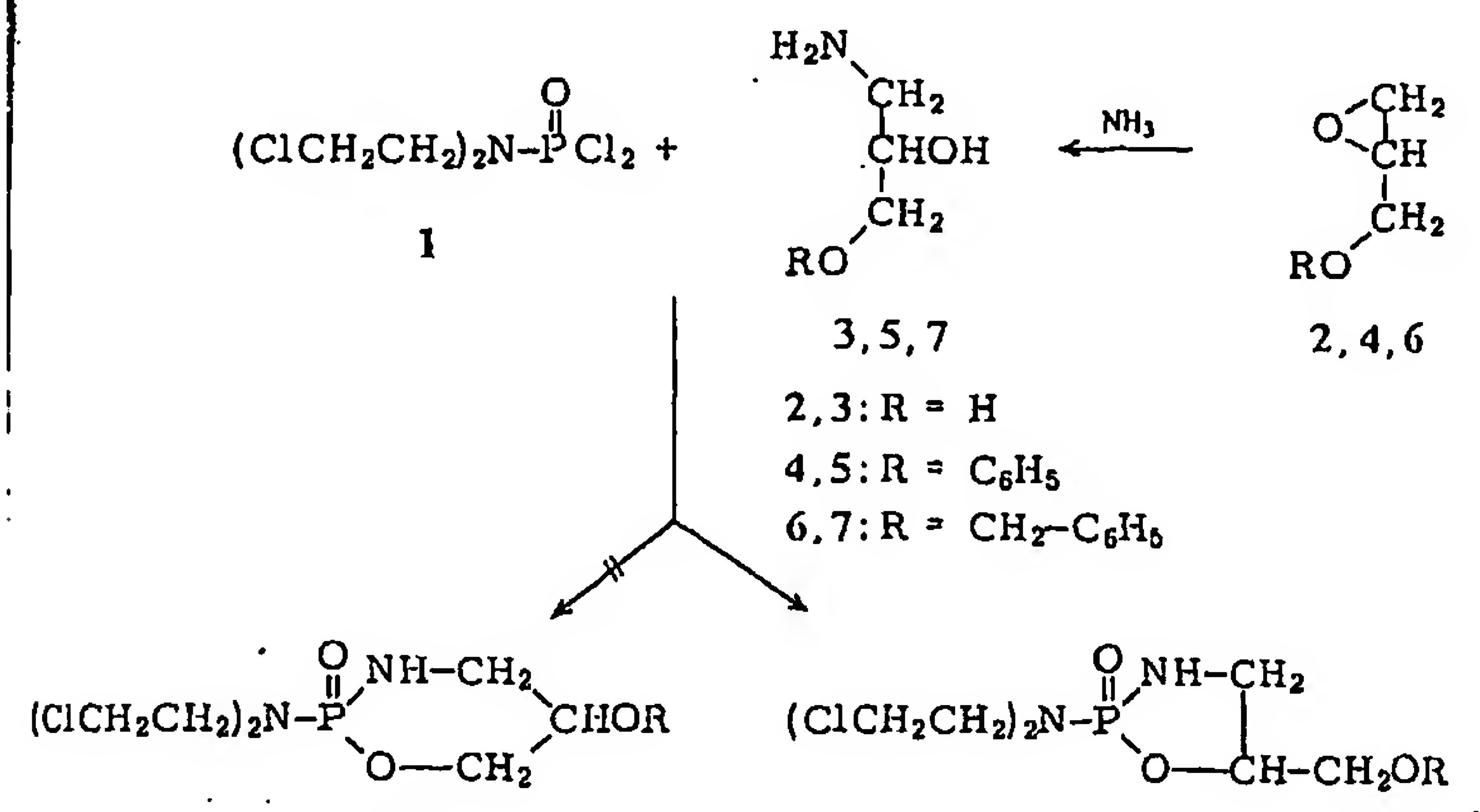
Es hat in der Vergangenheit nicht an Versuchen gefehlt, die therapeutische Wirksamkeit von Cyclophosphamid (CP) zu verbessern. Dies geschah einmal durch Abwandlung des Grundgerüstes im Cyclophosphamid[2-7], zum anderen durch Stabilisierung der durch metabolische Aktivierung gebildeten Zwischenstufen[8]. Da die metabolische Aktivierung von CP an C-4 erfolgt[9] und ein Methyl-Substituent an C-5 die therapeutische Wirksamkeit von CP nur geringfügig beeinflußt[10,11] bietet sich diese Position zur Verknüpfung mit geeigneten Carrier-Systemen für die Verbesserung der therapeutischen Aktivität an. Aus diesen Überlegungen heraus haben wir uns zum Ziel gesetzt, 5-Hydroxyendoxan darzustellen, um über dessen funktionelle Gruppe geeignete Trägermoleküle anzuknüpfen. 5-Chlor- und 5-Brom-Derivate sind bereits dargestellt worden[12]. Im Folgenden berichten wir über die bisherigen Versuche zur Darstellung dieser Verbindung.

Die präparativ einfachste Möglichkeit zur Darstellung von 5-Hydroxyendoxan stellt die Umsetzung von Phosphamidichlorid **1** mit 1-Aminopropan-2,3-diol (**3**) dar. Es ist jedoch nicht sicher, daß es zur Bildung des 6-Ringes **8** kommt, sondern es kann auch der 5-Ring **9** gebildet werden. Führt man die Umsetzung in Gegenwart von Et_3N in CH_2Cl_2 durch, so lassen sich nach sc Reinigung an SiO_2 zwei Verbindungen isolieren, bei denen es sich nach Analyse und MS um Isomere handeln muß (bis zur Strukturordnung als A und B bezeichnet). Die Analyse der ^{1}H-NMR-Spektren läßt keine Entscheidung zu, ob es sich um diastereomere Verbindungen von **8** oder **9** oder um **8** und **9** handelt. Auch die ^{13}C-Spektren ließen aufgrund fehlender Vergleichsverbindungen keine Entscheidung zu. Der Versuch durch Acetylierung der freien OH-Gruppe zu **10/11** die chemische Verschiebung der Protonen im Sinne einer besseren Interpretation zu bewirken, war nicht erfolgreich. Zur Lösung dieses Problems war es notwendig, entweder eine Verbindung des Typs **8** oder **9** auf unabhängigem Wege dazustellen. Präparativ ist es bedeutend einfacher, Verbindungen des Typs **9** darzustellen, da Arylether des Typs **5** oder **7** durch Umsetzung der Glycidether **4** oder **6**[13] mit NH_3 leicht zugänglich sind, und deren Reaktionen mit Phosphamiddichlorid **1** eindeutig Verbindungen **12** bzw. **14** liefern sollten. Hydrierung ergäbe dann eine oder zwei diastereomere Verbindungen **9**.

Wir haben zunächst den Arylether **5**[13] eingesetzt, da er wesentlich leichter zugänglich ist. Auch bei dieser Umsetzung entstehen zwei Verbindungen in äquimol. Mengen, bei denen es sich um die beiden diastereomeren Phenylether **12** handelt, die sich problemlos chromatographisch voneinander trennen lassen. Bei der katalytischen Hydrierung konnte jedoch bei keinem der beiden Diastereomeren eine Spaltung der Ether-Bindung erreicht werden. Als Reaktionsprodukte ließen sich in guten Ausbeuten die Cyclohexylether **13** erhalten. Der Versuch, die Etherbindung durch Säurekatalyse zu spalten, führte zur Zersetzung.

Aufgrund dieses Mißerfolges haben wir dann den Benzylether **7**[14] dargestellt und mit **1** umgesetzt. Auch hier entstanden zwei isomere Verbindungen **14** in äquimol. Mengen. Hier verlief die Hydrierung unter Pd/C-Katalyse in der erwarteten Weise. Jedes Isomer lieferte einen Alkohol **9** (bis zur Strukturzuordnung als X und Y bezeichnet), deren IR-Spektren (KBr) mit den IR-Spektren (KBr) der Reaktionsprodukte aus **1** und **3** verglichen wurden. Der Vergleich zeigt, daß das Isomer A aus dieser Umsetzung mit dem Isomer X nach der Hydrierung identisch ist. Das Isomer B und das Isomer Y zeigten in den IR-Spektren strukturelle Ähnlichkeiten, waren jedoch nicht identisch. Die Hoffnung, daß es sich bei dem Isomer B um eine isomere Verbindung **8** han-



1; 3,5,7; 2,4,6

2,3: R = H
4,5: R = C_6H_5
6,7: R = CH_2–C_6H_5

8,10; 9, 11, 12-14

8,9 R = H
10,11 R = $OCOCH_3$

12: R = C_6H_5
13: R = c-C_6H_{11}
14: R = CH_2–C_6H_5

delt, erwies sich als trügerisch. Die IR-Spektren in Lösung zeigten die Identität von Isomer B und Isomer Y. Offensichtlich kann **9** in unterschiedlichen Kristallgittern kristallisieren, so daß die IR-Spektren in KBr Unterschiede zeigen. Aufgrund dieser Ergebnisse darf vermutet werden, daß es sich bei den Phenylethern **12** um die zu **14** analogen Verbindungen handelt.

Damit ist klar, daß die direkte Umsetzung von **1** und **3** nur die beiden diastereomeren Verbindungen **9** liefert, ein Verhalten, das aus thermodynamischen Gründen erklärbar ist. Die Festlegung der absoluten Stereochemie war aufgrund der vorliegenden Ergebnisse nicht möglich.

Experimenteller Teil

Schmp.: nach Dr. Tottoli (unkorr.) *^{1}H-NMR* und *^{13}C-NMR*: Bruker WK 70, TMS int. Stand., δ-Skala. *Elementaranalysen*: Max-Planck-Institut für Med. Forschung, Heidelberg. *DC*: Kieselgel 60 F_{254} der Fa. Merck, Darmstadt. Kammersättigung, Detektion UV-Licht 254 nm oder Iodkammer. *Sc*: Kieselgel der Fa. Merck, Darmstadt. Fließmittel: Angaben in v:v.

Umsetzung von Phosphamiddichlorid 1 *mit 1-Aminopropan-1,3-diol* (3). 1.82 g (20 mmol) 1-Amino-propan-2,3-diol und 4.2 g (40 mmol) Et_3N wurden in 30 ml DMF gelöst und unter Kühlung auf 0° 5.16 g (20 mmol) Dichlorid **1** in kleinen Portionen zugegeben. Anschließend wurde über Nacht bei Raumtemp. gerührt. Das DMF wird i. Vak. abgezogen und der Rückstand mit CH_2Cl_2 ausgezogen. SC an Kieselgel $CHCl_3$/EtOH 9:1. Fr. 22–29, Schmp. 98° (Ether) Isomer A, 1.6 g (5.8 mmol, 29 % d. Th.). $C_7H_{15}Cl_2N_2O_3P$ (276.0) Ber. C 30.4 H 5.46 N 10.1 Gef. C 30.7 H 5.85 N 9.7.
^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.93 (1H, d, breit, mit D_2O austauschbar); 3.05 (1H, d, breit, mit D_2O austauschbar); 3.45 (6H, m); 3.65 (6H, m); 3.87 (1H, d); 4.54 (1H, m). m/e 276 für $C_7H_{15}Cl_2N_2O_3PCl_2$; IR (KBr) (cm^{-1}) 3370, 3300, 2890, 1410, 1235, 1195, 1100, 1035, 800, 665. ^{13}C-NMR (/D_6/-DMSO): δ (ppm) = 42.37 (t, CH_2-N); 43.02 (t), 43.11 (t) 48.22 (t), 48.41 (t) N-CH_2-CH_2Cl; 62.71 (t, CH_2-O); 78.38 (d, CH-O). Fr. 35–46, Schmp. 75° (Ether) Isomer B, 1.4 g (5.0 mmol, 25 % d. Th.). $C_7H_{15}Cl_2N_2O_3P$ (276.0) Ber. C 30.4 H 5.46 N 10.1 Gef. C 30.7 H 5.60 N 9.8

^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.84 (1H, d, mit D_2O austauschbar); 3.44 (6H, m); 3.65 (6H, m); 3.68 (1H, d, breit, mit D_2O austauschbar); 3.90 (1H, d); 4.68 (1H, s, breit). IR (KBr) (cm^{-1}) 3300, 2940, 1435, 1310, 1230, 1095, 1020, 990, 935, 800, 670; IR(CCl_4) (cm^{-1}) 3440, 1450, 1345, 1230, 1085, 980, 925; ^{13}C-NMR (/D_6/-DMSO): δ (ppm) = 42.37 (t, CH_2-N); 43.41 (t), 43.74 (t), 48.29 (t), 48.48 (t), N-CH_2-CH_2Cl; 61.93 (t, CH_2-O); 77.01 (d, CH-O).

Acetylierung der Isomere A und B. 276 mg (1 mmol) der Isomere A und B wurden in je 10 ml Pyridin gelöst, unter Eiskühlung 1 ml Acetanhydrid zugegeben und über Nacht bei RT stehen gelassen. Die Ansätze wurden auf Eiswasser gegossen und mit CH_2Cl_2 ausgeschüttelt. Die vereinigten organischen Phasen wurden mit gesättigter Hydrogencarbonat-Lösung und mit Wasser gewaschen. Der nach dem Einengen verbleibende Rückstand wurde an Kieselgel chromatographiert. ($CHCl_3$/EtOH 15:1).

Isomer A Acetat. 265 mg (0.82 mmol, 82 % d. Th), Schmp. 95° (Ether). $C_9H_{17}Cl_2N_2O_4P$ (318.0) Ber. C 33.9 H 5.37 N 8.8 Gef. C 34.1 H 5.44 N 8.6. ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.15 (3H, s); 3.15 (1H, d, breit, mit D_2O austauschbar); 3.20–3.80 (10H, m); 4.27 (2H, m); 4.65 (1H, m).

Isomer B Acetat. 230 mg (0.7 mmol, 70 % d. Th.), Schmp. 90° (EtOH). $C_9H_{17}Cl_2N_2O_4P$ (318.0) Ber. C 33.9 H 5.37 N 8.8 Gef. C 34.0 H 5.44 N 8.7. ^{1}H-NMR ($CDCl_3$); δ (ppm) = 2.13 (3H, s); 3.05–3.80 (11H, m, 1H mit D_2O austauschbar); 4.25 (2H, d); 4.87 (1H, m).

Umsetzung von Phosphamidichlorid **1** *mit* **5**

2.59 g (10 mmol) **1** wurden in 20 ml absol. Toluol vorgelegt und 1.67 g (10 mmol) **5**[13] mit 2.1 g (20 mmol) Et_3N in 20 ml Toluol zugetropft. Nach 48 Std. bei RT. wurde die org. Phase mit 2 N-HCl und H_2O ausgeschüttelt und getrocknet. Der nach dem Einengen verbleibende Rückstand von **12** wurde an Kieselgel chromatographiert. ($CHCl_3$/EtOH 9:1).

Fr. 1–4 Schmp. 113° (EtOH), **12** Isomer I, 0.95 g (2.7 mmol, 27 % d. Th.). $C_{13}H_{19}Cl_2N_2O_3P$ (352.1) Ber. C 44.2 H 5.43 N 7.9 Gef. C 44.6 H 5.22 N 8.1.

^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.20–3.80 (11H, m, 1H mit D_2O austauschbar); 4.15 (2H, m), 4.13 (1H, m); 6.80–7.40 (5H, m). ^{13}C-NMR ($CDCl_3$): δ (ppm) = 42.31 (t, CH_2-N); 44.32 (t), 44.71 (t); 49.13 (t) 49.39 (t, N-CH_2-CH_2Cl); 68.89 (t, CH_2O); 75.91 (d, CH-O); 114.77 (d), 121.66 (d), 129.72 (d, C-aromat.).

Fr. 6–11, Schmp. 109° (EtOH), **12** Isomer II, 1.02 g (2.9 mmol, 29 % d. Th). $C_{13}H_{19}Cl_2N_2O_3P$ (352.1) Ber. C 44.2 H 5.43 N 7.9 Gef. C 44.4 H 5.28 N 7.7.

^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.25–3.80 (11H, m) 3.90–3.40 (2H, m) 4.87 (1H, m); 6.85–7.45 (5H, m). ^{13}C-NMR ($CDCl_3$): δ (ppm) = 42.30 (t, CH_2-N); 43.80 (t); 44.13 (t); 49.07 (t); 49.33 (t) N-CH_2CH_2Cl; 67.72 (t, CH_2-O); 75.00 (t, CH_2-O); 114.64 (d); 121.73 (d); 129.79 (d); C-aromat.

Hydrierungen von **12** *Isomer I und Isomer II.* 352 mg (1 mmol) der Arylether (Isomer I und Isomer II) wurden in 30 ml EtOH mit 200 mg Pt hydriert. Nach dem Einengen SC an SiO_2 ($CHCl_3$/EtOH 15:1). **13** Isomer I, Schmp. 78° (Ether) 310 mg (0.78 mmol, 78 % d. Th.). $C_{13}H_{25}Cl_2N_2O_3P$ (358.1) Ber. C 43.5 H 7.02 N 7.8 Gef. C 43.2 H 7.10 N 7.6. ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.00–2.20 (11H, m); 3.15 (1H, d, breit, mit D_2O austauschbar), 3.20–3.85 (12H, m); 4.53 (1H, m).

13 Isomer II, Schmp. 75° (Ether) 320 mg (0.89 mmol 89 % d. Th.). $C_{13}H_{25}Cl_2N_2O_3P$ (358.1) Ber. C 43.5 H 7.02 N 7.8 Gef. C 43.7 H 7.65 N 7.7. ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.00–2.20 (11H, m); 3.07 (1H, d, breit, mit D_2O austauschbar); 3.15–3.85 (12H, m); 4.67 (1H, m).

Darstellung der Benzylether **6** *und* **7**.

Die in der Lit.[14] angegebene Vorschrift erwies sich als nicht sehr ergiebig. Wir haben sie daher wie folgt abgewandelt: 2.3 g Na (0.1 g-Atom) wurden in 20 ml Benzylalkohol gelöst und durch Zugabe von 60 ml Acetonitril das entstandene Alkoholat suspendiert. Nach Zutropfen von 9.2 g (0.1 mmol) Epichlorhydrin in 20 ml Acetronitril wurde 12 Std. bei 60° gehalten. Nach Filtration und Einengen wurde der Rückstand dest. Sdp. 0.2 70°. Ohne weitere Reinigung wurde mit konz. NH_3 im Druckgefäß 3 d bei R. T. gerührt.

Das nach dem Abdampfen verbliebene Öl kristallisierte nach einigen Tagen. Schmp. von 7 35–40°.

Die Umsetzung des Benzylethers 7 mit 1 wurde analog dem Phenylether durchgeführt. SC an Kieselgel $CHCl_3$/EtOH 30:1. Fr. 5–7, **14** Isomer X, 1.2 g (3.25 mmol, 32 % d. Th.) Öl. $C_{14}H_{21}Cl_2N_2O_3P$ (367.1) Ber. C 45.8 H 5.77 N 7.6 Gef. C 46.2 H 5.81 N 7.1.

^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.10 (1H, d, breit, mit D_2O austauschbar) 3.20–3.80 (12H, m), 4.55 (1H, m), 4.63 (2H, s), 7.33 (5H, s).

Fr. 12–15, **14** Isomer Y, 930 mg (2.5 mmol, 25 % d. Th.) Öl. $C_{14}H_{21}Cl_2N_2O_3P$ (367.1) Ber. C 45.8 H 5.77 N 7.6 Gef. C 45.7 H 6.01 N 7.5.

^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.10 (1H, d breit, mit D_2O austauschbar), 3.20–3.80 (12H, m), 4.60 (2H, s), 4.13 (1H, m), 7.33 (5H, s).

Hydrierungen der Benzylether **14**: Je 1 mmol von Fraktion 5–7 und Fraktion 12–16 wurden jeweils mit 100 mg Pd/C in EtOH hydriert. Die Reinigung der Alkohole erfolgte durch SC an Kieselgel ($CHCl_3$/EtOH 4:1). **9**, Isomer X. 235 mg (0.85 mmol, 85 % d. Th.). Schmp. 99° (Ether). $C_7H_{15}Cl_2N_2O_3P$ (276.0) Ber. C 30.4 H 5.46 N 10.1 Gef. C 30.4 H 5.46 N 10.0.

IR (KBr) cm^{-1}, 3370, 3300, 2890, 1410, 1235, 1195, 1100, 1035, 800, 665. ^{1}H-NMR ist identisch mit Isomer A. **9**, Isomer Y, 195 mg (0.7 mmol, 70 % d. Th.). Schmp. 63° (Ether), $C_7H_{15}Cl_2N_2O_3P$ (276.0) Ber. C 30.4 H 5.46 N 10.1 Gef. C 30.3 H 5.33 N 9.7.

IR (KBr) cm^{-1} 3260, 2940, 1430, 1340, 1230, 1200, 1085, 990, 920, 780, 660; IR (CCl_4) cm^{-1} 3440, 1450, 1345, 1230, 1085, 980, 925; ^{1}H-NMR ist identisch mit Isomer B.

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Short Communication

Rapid synthesis of 2-desoxy-2-amino-3-phosphocholine-glycerinic-acid-alkylester, 1-alkyl-1-desoxy- and 1-*O*-alkyl-2-desoxy-2-amino-*sn*-glycero-3-phosphocholines, -3-phospho-*N*,*N'*-dimethylethanolamine and -3-phospho-Fmoc-serine-methylester

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A convenient sequence for the rapid synthesis of 2-desoxy-2-amino-3-phosphocholine-glycerinic-acid-alkylester, 1-alkyl-1-desoxy- and 1-*O*-alkyl-2-amino-2-desoxy-3-phospho- derivatives is described. Key steps are the reaction of 1-carbonyloxyalkyl-, 1-alkyl- or 1-*O*-alkyl-amino-alcohols with phosphorus oxychloride to 1-carbonyloxyalkyl-, 1-alkyl- or 4-substituted 2-chloro-2-oxo-1,3,2-oxazaphospholane followed by nucleophilic displacement with choline tosylate, 1-bromoethane-2-ol or Fmoc-L-serine-methylester and subsequent hydrolysis to 2-amino-lysophospholipids giving the desired compounds in yields ranging between 68% and 81%. Several 2-amino-lysophospholipid analogs can then be prepared by this synthetic scheme utilizing the same oxazaphospholane intermediate. A brief method for the preparation of 2-amino-3-hydroxy-propionic-acid-pentyl- and -octylester from L-serine is described, opening a facile access to chiral precursors of phospholipid analogs.

Key words: ether lipid; phospholipid; 2-desoxy-2-amino-*sn*-glycerophospholipids; 2-amino-lysophospholipid analogs

Introduction

Phospholipid analogs containing an acylamino linkage instead of an ester bond at position 2 show strong competitive inhibition of phospholipases [1–3] and are useful tools for the crystallization of stable enzyme inhibitor complexes [4]. Systematic variation of the C-1-alkyl substituent revealed an optimum of the inhibitory power of short alkyl chains for porcine pancreatic phospholipase A_2 [5].

Our interest in the synthesis of novel phospholipase inhibitors made us focus on the convenient preparation of short-chain 1-carbonyloxyalkyl-, 1-alkyl-1-desoxy- or 1-*O*-alkyl analogs of 2-amino-lysophospholipids allowing the subsequent derivatization and condensation with various reagents and thus the synthesis of 2-desoxy-2-amino-phospholipids bearing labile groups at the *sn*-2 position.

Previous syntheses of 2-desoxy-2-amino-*sn*-glycerophospholipids, starting from serine-derived 2-aminopropane-1,3-diol or from other amino-alcohols, involve an initial acetylation of the amino group and subsequent introduction of the phosphocholine moiety [6]. The lyso compounds can then be obtained by desacetylation of the 2-*N*-acetylaminophospholipid [6].

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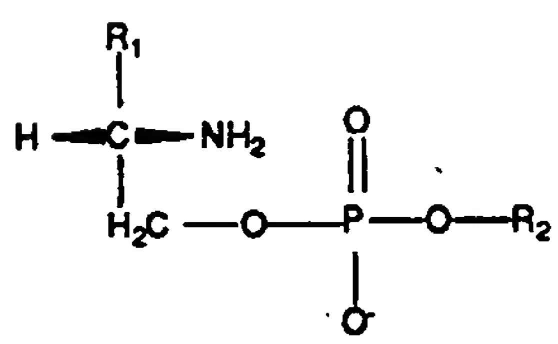
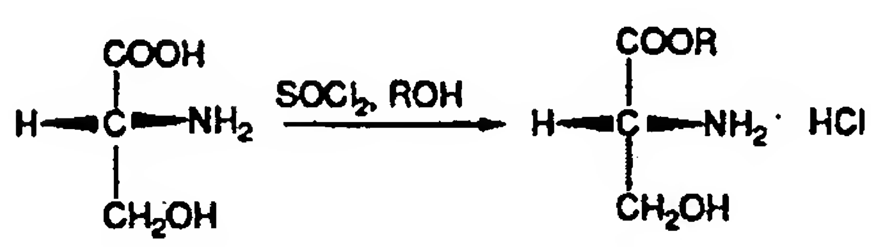
We report here a novel method for the rapid preparation of 2-amino-lysophospholipids, suitable for the preparation of *sn*-1-carbonyloxyalkyl analogs, -1-alkyl-1-desoxy- or -1-*O*-alkyl-phospholipids. We have found it most convenient to obtain 1-carbonyloxyalkyl-, 1-alkyl-1-desoxy- or 4-substituted 2-chloro-2-oxo-1,3,2-oxazaphospholane, a key synthetic intermediate in one step from L-serine-derived aminoalcohols as chiral precursors.

Nucleophilic displacement of the chlorine in the parent compounds and subsequent ring opening directly yielded the desired 2-desoxy-2-amino-*sn*-glycero-phosphocholines. In order to further investigate the scope and the general use of this procedure we have tested several nucleophiles for ring



	R_1	R_2
17	$-COOC_5H_{11}$	$-(CH_2)_2N^+(CH_3)_3$
18	$-COOC_8H_{17}$	$-(CH_2)_2N^+(CH_3)_3$
19	$-(CH_2)_3-CH_3$	$-(CH_2)_2N^+(CH_3)_3$
20	$-CH_2-O-C_8H_{17}$	$-(CH_2)_2N^+(CH_3)_3$
21	$-CH_2-O-C_{10}H_{21}$	$-(CH_2)_2N^+(CH_3)_3$
29	$-CH_2-O-C_{10}H_{21}$	$-(CH_2)_2N(CH_3)_2$
32	$-CH_2-O-C_{10}H_{21}$	$-CH_2-CH(NH\text{-}Fmoc)(COOCH_3)$

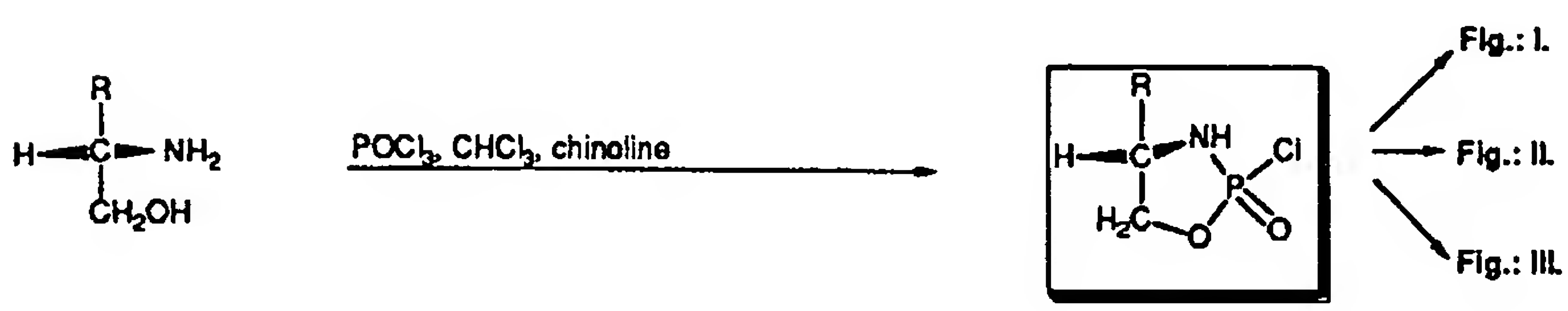
SCHEME:



1

2: $R = C_5H_{11}$

3: $R = C_8H_{17}$



2: $R = -COOC_5H_{11}$ HCl (2-amino-3-hydroxy-propionic-acid-pentylester-hydrochloride)

3: $R = -COOC_8H_{17}$ HCl (2-amino-3-hydroxy-propionic-acid-octylester-hydrochloride)

4: $R = -(CH_2)_3CH_3$ (2-amino-hexane-1-ol)

5: $R = -CH_2-O-C_8H_{17}$ (1-O-octyl-2-amino-propane-3-ol)

6: $R = -CH_2-O-C_{10}H_2$ (1-O-decyl-2-amino-propane-3-ol)

7: $R = -COOC_5H_{11}$

8: $R = -COOC_8H_{17}$

9: $R = -(CH_2)_3-CH_3$

10: $R = -CH_2-O-C_8H_{17}$

11: $R = -CH_2-O-C_{10}H_{21}$

Scheme 1. Synthesis of 4-substituted 2-chloro-2-oxo-1,3,2-oxazaphospholane intermediates.

opening (e.g., Fmoc-serine-methylester) leading to the respective 2-aminophospholipid analogs.

To shortcut the preparation of chiral aminoalcohols as precursors for lysoaminophospholipids we have also developed a brief one-step synthesis of short-chain aminoalcohols (2-amino-3-hydroxy-propionic-acid-pentyl- and -octylester) which is outlined below.

Experimental

Materials

L-Serine, DL-norleucine, chinoline, choline (50% in water), dimethylamine, tetrabutylammonium iodide and toluene were purchased from Fluka (Buchs, CH).

1-Pentanol, phosphorus oxychloride, pyridine and 2-bromoethane-1-ol were obtained from Aldrich (Steinheim, Germany).

1-Octanol, *p*-toluenesulfonic acid, acetic acid (100%), acetanhydride, triflouracetic anhydride, 2-propanol and lithiumaluminiumhydride were products of E. Merck (Darmstadt, Germany).

Diethylether was obtained from Roth (Karlsruhe, Germany), chloroform and methanol were purchased from J.T. Baker (Deventer, Holland), Fmoc chloride was a product of Bachem (Heidelberg, Germany). Thionyl chloride and tetrahydrofuran were purchased from Riedel-de Haen (Seelze, Germany).

Choline toluenesulfonate, 1-*O*-octyl-2-amino-propane-3-ol and 1-*O*-decyl-2-amino-propane-3-ol were prepared as described previously [6,7]. Silica gel (grade 60,70–230 mesh) for column chromatography and precoated silica gel TLC plates (0.25 mm, F 254) were purchased from Machery-Nagel (Düren, Germany).

General methods

Chloroform (b.p. 61°C) and methanol (b.p. 65°C) were distilled from P_2O_5 and from KOH respectively, prior to use. Thionyl chloride (b.p. 78–79°C) was purified by distillation from linseed-oil. All reactions were carried out under a nitrogen atmosphere.

Thin-layer chromatography was performed on silica gel plates using a mixture of chloroform/methanol/water (30:20:5; v/v) as mobile phase. The following detecting methods were used: amines were checked with ninhydrin (1.5% in methanol), while phosphorus -containing compounds were detected with 'Phospray' (Supelco, Bad Homburg, Germany).

For silica gel column chromatography a flow rate of 2.5 ml/min was generally used. Phosphorus-containing compounds and amines were detected as described above.

HPLC chromatography was carried out on a Milton Roy HPLC system (consta Metric 3000 and consta Metric III pumps, spectro Monitor D detector, CI-4100 integrator, GM 4000 gradient programmer) using a Lichrospher 100 CN column, 10 μm (LiChro-CART 250-10, E. Merck, Darmstadt, Germany). Melting points were determined with a 'Stereo Star' melting block (Reichert-Jung, Austria).

Accurate mass spectra were obtained using a MAT 311 A mass spectrometer (Varian, Bremen, Germany) equipped with a FAB ion gun (Xe, 6 kV, 1 mA ion current; Ion Tech, Teddington, UK). Spectra were obtained using FAB-ionization unless stated otherwise. Glycerol and nitrobenzylalcohol were used as matrices for FAB ionization.

All ^{1}H-NMR spectra were recorded at 250 MHz while all ^{13}C-NMR spectra were performed at 62.89 MHz on WM-spectrometer (Bruker Physik AG, Karlsruhe, Germany) using tetramethylsilane as an internal reference. Spectra were run in methanol-d_4 or in a mixture of chloroform-*d*/methanol-d_4 (2:1, v/v). Multiplicities are reported as singlet (s), doublet (d), triplet (t) or multiplet (m).

Specific rotations were determined with a Perkin Elmer 243 polarimeter (Überlingen, Germany) using a 0.1-dm cell.

L-Serine-pentyl- (2) *and -octylester* (3)

These compounds were prepared utilizing the method published for the preparation of L-serine-methylester [8] with the following deviations. To 250 mmol of alcohol (pentanol or octanol) in a flame-dried 100-ml three-necked flask, equipped with a magnetic stirrer, 2.6 ml (35.6 mmol) thionylchloride were added within 3 min (the temperature did not exceed 25°C) and stirring was

continued for another 12 h at room temperature. After the addition of 1.05 g (10 mmol) of L-serine (**1**) the temperature was raised to 70°C for the pentylester (**2**) (to 80°C for the respective octyl ester (**3**)) and stirred for 12 h. The mixture was then kept at room temperature for an additional 12-h period. The surplus alcohol was removed by distillation in vacuo. The L-serine esters (**2**) and (**3**) were precipitated as hydrochlorides by the addition of diethylether (50 ml). After filtration and drying we obtained the respective L-serine ester in 98% yield ((**2**) L-serine-pentylester-hydrochloride, $C_8H_{18}Cl_1N_1O_3$ (211.69), 2.07 g, (**3**) L-serine-octylester-hydrochloride, $C_{11}H_{24}Cl_1N_1O_3$ (253.77), 2.48 g).

TLC: R_f (**2**) 0.70; (**3**) 0.80.

m.p.: (**2**) 70–71°C; (**3**) 72–73°C.

CHN analysis: (**2**) found: C 44.75%, H 8.59%, N 6.47%; calculated: C 45.39%, H 8.57%, N 6.62%; (**3**) found: C 52.30%, H 9.57%, N 5.53%; calculated: C 52.06%, H 9.53%, N 5.52%.

Mass spectrum: (**2**) 70 keV, EI-ionization: *m/z* 176 (MH^+; 100%), 106 (9.5%), 88 (3%), 60 (35%), 43 (15%); (**3**) 70 keV, EI-ionization: *m/z* 218 (MH^+; 100%), 106 (19%), 88 (3%), 60 (29%), 43 (17.5%).

^{1}H-NMR: (**2**) δ 4.2 (2H, t, $-N\underline{H}_2$), 4.1 (1H, m, *sn*$-2-C\underline{H}$), 4.0 (2H, m, $C\underline{H}_2-OH$), 1.7 (2H, m, $-O-C\underline{H}_2-CH_2$), 1.3 (4H, m, $(C\underline{H}_2)_2-CH_3$), 0.9 (3H, t, $-CH_2C\underline{H}_3$); (**3**) δ 4.2 (2H, t, $-N\underline{H}_2$), 4.1 (1H, m, *sn*$-2-C\underline{H}$), 4.0 (2H, m, $C\underline{H}_2-OH$), 1.7 (2H, m, $-O-C\underline{H}_2-CH_2$), 1.3 (12H, m, $(C\underline{H}_2)_6-CH_3$), 0.9 (3H, t, $-CH_2-C\underline{H}_3$).

$[\alpha]_D^{20}$: (**2**) -5.3° (*c* 1.00, CH_3OH); (**3**) -5.0° (*c* 1.00, CH_3OH).

2-Amino-hexane-1-ol (**4**)

A 2.6-ml aliquot (35.6 mmol) of thionyl chloride was added dropwise to 10 ml (247 mmol) of methanol (100-ml three-necked flask, magnetic stirrer; temperature did not exceed 25°C). Then 1.31 g (10 mmol) of DL-norleucine was added and stirring was continued for 24 h at room temperature. After removing the surplus methanol in vacuo, the residue was dissolved in 10 ml methanol, then diethylether (50 ml) was added and the DL-norleucine-methylester-hydrochloride was precipitated in 98% yield (TLC: R_f 0.67). After filtering and drying 1.82 g (10 mmol) of DL-norleucine-methylester-hydrochloride was suspended in tetrahydrofuran (THF) at 0°C. 1.9 g (50 mmol) of lithiumaluminiumhydride ($LiAlH_4$) was added within 3 min. The temperature was raised to 70°C for 8 h and the mixture stirred for 12 h at room temperature. The surplus reducing agent was destroyed by reaction with humide ether and then with water. Tetrahydrofuran was removed in vacuo and the aquous layer extracted three times with chloroform. After concentration, the crude 2-amino-hexane-1-ol (**4**) was obtained in 84% yield.

1-Carbonyloxy-pentyl-, -octyl-, 1-butyl- and 1-O-octyl-, -O-decyl-2,3-(2'-chloro-2'-oxo-1', 3', 2'-oxazaphospholane) (**7**)–(**11**)

To 1.17 ml (12.5 mmol) of phosphorus oxychloride a solution of 2.11 g (10 mmol) 2-amino-3-hydroxy-propionic-acid-pentylester-hydrochloride (**2**) (2.53 g (10 mmol) 2-amino-3-hydroxy-propionic-acid-octylester-hydrochloride (**3**), 1.17 g (10 mmol) 2-amino-hexane-1-ol (**4**), 2.03 g (10 mmol) 1-*O*-octyl-2-amino-propane-3-ol (**5**) or 2.31 g (10 mmol) 1-*O*-decyl-2-aminopropane-3-ol (**6**)), respectively and 2.96 ml (25 mmol) of quinoline in 40 ml dry chloroform was added dropwise at 0°C. The mixture was allowed to come to room temperature and stirred further for 2 h at 50°C. The solutions of the crude products (**7**)–(**11**) were used in the next step without further purification.

2-Desoxy-2-amino-3-phosphocholine-glycerinic-acid-pentyl- and -octylester, 1-butyl-1-desoxy- and 1-O-octyl-, -O-decyl-2-desoxy-2-amino-sn-glycero-phosphocholines (**17**)–(**21**)

A solution of 7 ml (86.5 mmol) of dry pyridine, 6.03 g (22 mmol) of choline tosylate and 1.1 g (3.0 mmol) of tetrabutylammonium iodide in 30 ml of chloroform was combined with the respective 4-substituted 2-chloro-2-oxo-1,3,2-oxazaphospholane (**7**)–(**11**) at room temperature and the temperature was raised to 50°C for 2 h. Stirring was continued for 12 h at room temperature. The solvent was removed under reduced pressure to give the intermediate oxazaphospholanes (**12**)–(**16**).

A solution of the oxazaphospholanes (**12**)–(**16**) in 20 ml 2-propanol/acetic acid (80%), 3:2, was stirred for 30 min at 50°C and for another 2 h at room temperature.

The solvent was removed and the residue was purified by column chromatography (300 ml of silica gel in a column of 5.5 cm diameter).

The elution was first carried out with 500 ml chloroform/methanol (10:1) and then with 250 ml methanol/chloroform/water (30:20:5) followed by 1200 ml methanol/water (4:1); 200-ml fractions of the final eluent were collected, containing the highest concentration of compound **(17)**–**(21)** in fraction 2–4.

Concentration in vacuo and freeze drying afforded the 2-aminophospholipids **(17)**–**(21)** as colourless solids ((**17**) $C_{13}H_{29}N_2O_6P_1$ (340.36) and (**18**) $C_{16}H_{35}N_2O_6P_1$ (382.44): 68% yield; (**19**) $C_{11}H_{27}N_2O_4P_1$ (282.32), (**20**) $C_{16}H_{37}N_2O_5P_1$ (368.46) and (**21**) $C_{18}H_{41}N_2O_5P_1$ (396.51): 81% yield).

All products were demonstrated to be homogenous by TLC: R_f **(17)** 0–0.2, **(18)** 0–0.2, **(19)** 0–0.2, **(20)** 0–0.2, **(21)** 0–0.21.

To facilitate the characterization of compounds **(17)**–**(21)**, the *N*-acetylderivatives **(22)**–**(26)** of the respective products were prepared. A solution of 5 mmol 2-amino-phosphocholine **(17)**–**(21)** in 20 ml chloroform was combined with 4.7 ml (50 mmol) acetanhydride and 4 ml (50 mmol) pyridine for 4 h at 50°C.

After concentration in vacuo and purification by column chromatography (200 ml silica gel, 3.5 cm column diameter, elution with 1.3 l methanol/chloroform/water 30:20:5 (v/v/v), 2.7 l methanol), the *N*-acetylated derivatives **(22)** $C_{15}H_{31}N_2O_7P_1$ (382.39), **(23)** $C_{18}H_{37}N_2O_7P_1$ (424.48), **(24)** $C_{13}H_{29}N_2O_5P_1$ (324.36), **(25)** $C_{18}H_{39}N_2O_6P_1$, (410.49) and **(26)** $C_{20}H_{43}N_2O_6P_1$ (438.55) were isolated from the methanol fraction in 84% yield.

TLC: R_f **(22)** 0.18, **(23)** 0.22, **(24)** 0.26, **(25)** 0.21, **(26)** 0.23.

CHN analysis: **(22)** found: C 44.84%, H 7.23%, N 6.96%; calculated, containing 1 mol water: C 44.99%, H 8.31%, N 6.99%; **(23)** found: C 48.63%, H 8.97%, N 6.12%; calculated, containing 1 mol water: C 48.86%, H 8.88%, N 6.33%; **(24)** found: C 46.52%, H 9.14%, N 7.84%; calculated, containing 0.75 mol water: C 46.21%, H 9.10%, N 8.29%; **(25)** found: C 49.07%, H 9.79%, N 6.19%; calculated, containing 1.75 mol water: C 48.91%, H 9.69%, N 6.34%; **(26)** found: C 49.91%, H 10.04%, N 5.65%; calculated, containing 2.25 mol water: C 50.14%, H 9.99%, N 5.85%.

Mass spectra: **(22)** *m/z* 383 (MH^+), 341, 269, 184, 104, 86, 58, 45; **(23)** *m/z* 425 (MH^+), 269, 184, 104, 86, 58; **(24)** *m/z* 325 (MH^+), 184, 104, 86, 58; **(25)** *m/z* 411 (MH^+), 351, 228, 184, 104, 86, 58, 43; **(26)** *m/z* 439 (MH^+), 379, 256, 104, 86, 58, 43.

^{1}H-NMR: **(22)** δ 4.2 (2H, m, $-C\underline{H}_2-CH_2-N^+(CH_3)_3$), 4.0 (1H, m, *sn*-2-$C\underline{H}$), 3.6 (4H, m, *sn*-3-$C\underline{H}_2$, $-C\underline{H}_2-N^+(CH_3)_3$), 3.2 (9H, s, $-N^+(C\underline{H}_3)_3$), 1.9 (3H, s, $-CO-C\underline{H}_3$), 1.6 (2H, m, $-O-C\underline{H}_2(CH_2)_2-CH_3$), 1.3 (4H, m, $-(C\underline{H}_2)_2-CH_3$), 0.9 (3H, t, $-CH_2-C\underline{H}_3$).

(23) δ 4.2 (2H, m, $-C\underline{H}_2-CH_2-N^+(CH_3)_3$), 4.0 (1H, m, *sn*-2-$C\underline{H}$), 3.6 (4H, m, *sn*-3-$C\underline{H}_2$, $-C\underline{H}_2-N^+(CH_3)_3$), 3.2 (9H, s, $-N^+(C\underline{H}_3)_3$), 1.9 (3H, s, $-CO-C\underline{H}_3$), 1.6 (2H, m, $-O-C\underline{H}_2-(CH_2)_6-CH_3$), 1.3 (12H, m, $-(C\underline{H}_2)_6-CH_3$), 0.9 (3H, t, $-CH_2-C\underline{H}_3$).

(24) δ 4.2 (2H, m, $-C\underline{H}_2-CH_2-N^+(CH_3)_3$), 3.9 (1H, m, *sn*-2-$C\underline{H}$), 3.8 (2H, t, *sn*-3-$C\underline{H}_2$), 3.6 (2H, m, $-C\underline{H}_2-N^+(CH_3)_3$), 3.2 (9H, s, $-N^+(C\underline{H}_3)_3$), 1.9 (3H, s, $-CO-C\underline{H}_3$), 1.6 (2H, m, $-C\underline{H}_2-(CH_2)_2-CH_3$), 1.3 (4H, m, $-CH_2-(C\underline{H}_2)_2-CH_3$), 0.9 (3H, t, $-(CH_2)_3-C\underline{H}_3$).

(25) δ 4.2 (2H, m, $-C\underline{H}_2-CH_2-N^+(CH_3)_3$), 4.1 (1H, m, *sn*-2-$C\underline{H}$), 3.9 (2H, t, *sn*-3-$C\underline{H}_2$), 3.6 (2H, m, $C\underline{H}_2N^+(CH_3)_3$), 3.4 (2H, m, *sn*-1-$C\underline{H}_2$), 3.2 (9H, s, $-N^+(C\underline{H}_3)_3$), 1.9 (3H, s, $-CO-C\underline{H}_3$), 1.5 (2H, m, $-C\underline{H}_2-(CH_2)_6-CH_3$), 1.3 (12H, m, $-CH_2-(C\underline{H}_2)_6-CH_3$), 0.9 (3H, t, $-(CH_2)_7-C\underline{H}_3$).

(26) δ 4.2 (2H, m, $C\underline{H}_2-CH_2-N^+(CH_3)_3$), 4.1 (1H, m, *sn*-2-$C\underline{H}$), 3.9 (2H, t, *sn*-3-$C\underline{H}_2$), 3.6 (2H, m, $-C\underline{H}_2-N^+(CH_3)_3$), 3.45 (2H, m, *sn*-1-$C\underline{H}_2$-), 3.2 (9H, s, $-N^+(C\underline{H}_3)_3$), 2.0 (3H, s, $-CO-C\underline{H}_3$), 1.5 (2H, m, $-C\underline{H}_2-(CH_2)_8-CH_3$), 1.3 (16H, m, $-CH_2-(C\underline{H}_2)_8-CH_3$), 0.9 (3H, t, $-(CH_2)_9-C\underline{H}_3$).

$[\alpha]_D^{20}$: **(22)** -9.4° (*c* 1.00, CH_3OH); **(23)** -8.1° (*c* 1.00, CH_3OH); **(24)** -1.0° (*c* 1.00, CH_3OH); **(25)** -2.0° (*c* 1.00, CH_3OH); **(26)** -1.5° (*c* 1.00, $CHCl_3/CH_3OH$ 1:1).

1-O-decyl-2-N-acetyl-2-desoxy-sn-glycero-3-phospho-N,N'-dimethylethanolamine (30)

A solution of 7 ml (86.5 mmol) of dry pyridine and 3.0 g (24 mmol) of 1-bromoethane-2-ol in 20 ml of dry chloroform was combined with 3.11 g (10 mmol) of 4-decyloxy-methyl-2-chloro-2-oxo-

1,3,2-oxazaphospholane (**8**) and heated at 50°C for 12 h. Stirring was continued for 18 h at room temperature. The solvent was removed and the product (**27**) was used without further purification. Ring opening in a mixture of 20 ml 2-propanol/acetic acid (80%), 3:2, (30 min at 50°C, 2 h at room temperature) yielded 3.71 g (8.9 mmol) of crude 1-*O*-decyl-2-desoxy-2-amino-3-phosphoethyl-2′-bromide (**28**) (TLC: R_f 0.05–0.2). After concentration the residue was combined with a solution of 1.1 g (3 mmol) of tetrabutylammonium iodide (TBAI) and 4.03 g (10 mmol) of (**28**) in 20 ml of dry chloroform. Dimethylamine (6.74 ml, 100 mmol) was then added and the solution was stirred for 12 h at 50°C in a pressure bottle. The solvent and the excess dimethylamine were removed and the residue was purified by column chromatography as described for compounds (**17**)–(**21**). After concentration and freeze drying of fraction 1–3 of the methanol/water eluent we obtained the 1-*O*-decyl-2-desoxy-2-amino-3-phospho-*N*,*N*′-dimethylethanolamine (**29**) $C_{17}H_{38}N_2O_5P_1$ (381.47) in 74% yield. TLC: (**29**) R_f 0.19.

The *N*-acetyl-derivative (**30**) $C_{19}H_{40}N_2O_6P_1$ (423.52) was prepared for characterization as described above.

TLC: R_f (**30**) 0.45.

CHN analysis: found: C 49.91%, H 9.79%, N 6.01%; calculated, containing 2 mol water: C 49.66%, H 9.65%, N 6.10%.

Mass spectrum: (**30**) *m/z* 424 (MH^+), 256, 104, 86, 58, 43.

^{1}H-NMR: (**30**) δ 4.2 (2H, m, $-C\underline{H}_2-CH_2-N(CH_3)_2$), 4.1 (1H, m, *sn*$-2-C\underline{H}-$), 3.9 (2H, t, *sn*$-3-C\underline{H}_2-$), 2.9 (2H, m, $C\underline{H}_2-N(CH_3)_2$), 2.5 (6H, s, $-N(C\underline{H}_3)_2$), 2.1 (3H, s, $-CO-C\underline{H}_3$), 1.6 (2H, m, $-C\underline{H}_2-(CH_2)_6-CH_3$), 1.3 (16H, m, $-CH_2-(C\underline{H}_2)_8-CH_3$), 0.9 (3H, t, $-(CH_2)_7-C\underline{H}_3$).

$[\alpha]^{20}_D$: (**30**) −17.6° (*c* 1.00, CH_3OH).

1-O-decyl-2-desoxy-2-amino-3-phospho-Fmoc-serine-methylester (**32**)

The reaction of 3.11 g (10 mmol) of 4-*n*-decyloxy-methyl-oxazaphospholane (**11**) with 3.4 g (10 mmol) of Fmoc-L-serine-methylester was performed in the presence of 2 ml (24.8 mmol) of dry pyridine and 1.1 g (3.0 mmol) of tetrabutyl ammonium iodide (TBAI) in 10 ml of chloroform for 12 h at 50°C. The crude product (**31**) (TLC: R_f 0.25) was concentrated and used without further purification: a mixture of 20 ml 2-propanol/acetic acid (80%), 3:2, was added to the residue and the solution was stirred for 30 min at 50°C and for 2 h at room temperature. After removing the solvent we obtained the crude 1-*O*-octyl-2-desoxy-2-amino-3-phospho-Fmoc-serine-methylester (**32**) $C_{32}H_{46}N_2O_9P_1$ (633.70) in 81% yield. An analytical sample was prepared by HPLC chromatography (flow rate: 3 ml/min; gradient: from methanol/water 40:60 (v/v) to 100% methanol in 15 min; wavelength: 290 nm; retention time: 6.73 min).

TLC: R_f (**32**) 0.81.

CHN analysis: found: C 55.69%, H 7.82%, N 3.76%; calculated, containing 3 mol water: C 55.89%, H 7.62%, N 4.07%.

Mass spectrum: (**32**) *m/z* 635 (MH^+), 621, 105, 86, 57.

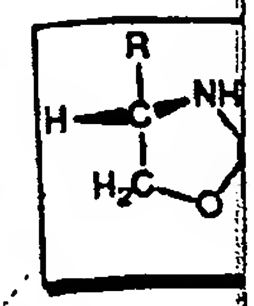
^{1}H-NMR: (**32**) δ 8.1–7.4 (8H, m, aromatic), 4.2 (2H, m, $-COO-C\underline{H}_2-CH-$), 4.0 (2H, m, $-P-O-C\underline{H}_2-CH-$), 3.9 (2H, m, *sn*$-2-C\underline{H}-$), 3.7 (2H, t, *sn*$-3-C\underline{H}_2-$), 3.6 (1H, m, $-COO-CH_2-C\underline{H}-$), 3.4 (2H, m, *sn*$-1-C\underline{H}_2$), 2.3 (3H, s, $-CO-C\underline{H}_3$), 1.5 (2H, m, $-O-CH_2-(C\underline{H}_2)_8-CH_3$), 1.25 (16H, m, $-(C\underline{H}_2)_8-CH_3$), 0.9 (3H, t, $(C_2)_9-C\underline{H}_3$).

$[\alpha]^{20}_D$: (**32**) −9.5° (*c* 1.00, $CHCl_3/CH_3OH$ 1:1).

Results and Discussion

Our interest in preparing 2-amino-lysophospholipid analogs has led us to explore a novel route to the synthesis of 1-carbonyloxyalkyl-, 1-alkyl-1-desoxy- and 1-*O*-alkyl-2-desoxy-2-amino-lysophospholipid derivatives. Hydrolysis of 2-(1, 2-diacyl-*sn*-glycero)-2-oxo-1′, 3′, 2′-oxazaphospholanes by 2-propanol/acetic acid is an established procedure to obtain *sn*-glycero-3-phosphoethanolamines (9).

It appeared attractive to us to apply this method to 2-substituted 4-carbonyl-oxyalkyl-, 4-alkyl- or 4-*n*-octyloxy-, -decyloxy-methyl-2-oxo-1,3,2-oxazaphospholanes (**12**)–(**16**), obtained from the corresponding chiral amino alcohols (**2**), (**3**), (**5**) and (**6**)((**4**) racemic) in two steps: the aminoalcohols (**2**)–(**6**) were reacted with phosphorus oxychloride



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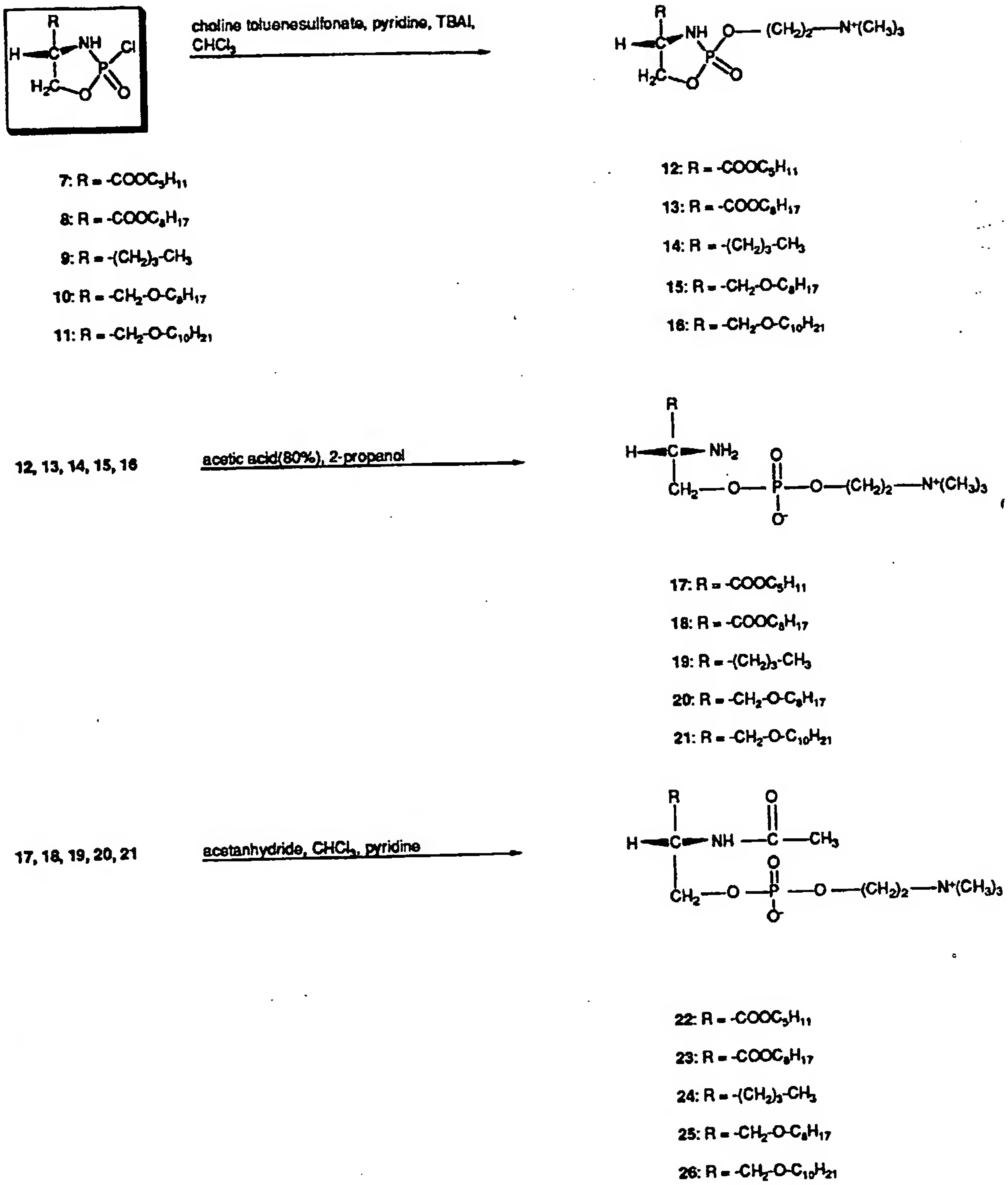

Fig. 1. Synthesis of 2-desoxy-2-amino-*sn*-glycero-3-phosphocholines.

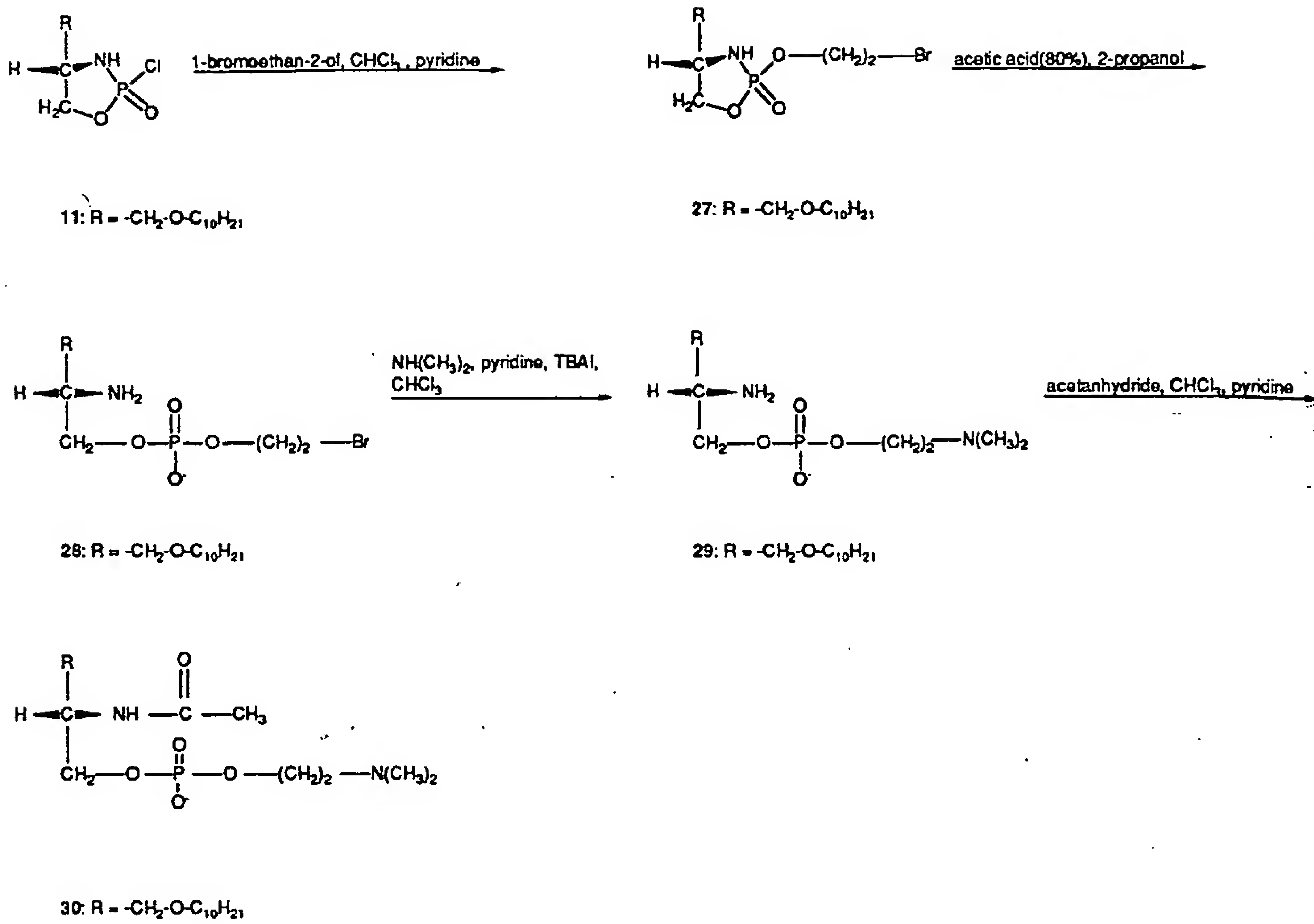

Fig. 2. Synthesis of 1-*O*-decyl-2-*N*-acetyl-2-desoxy-*sn*-glycero-3-phospho-*N*,*N'*-dimethyl-ethanolamine.

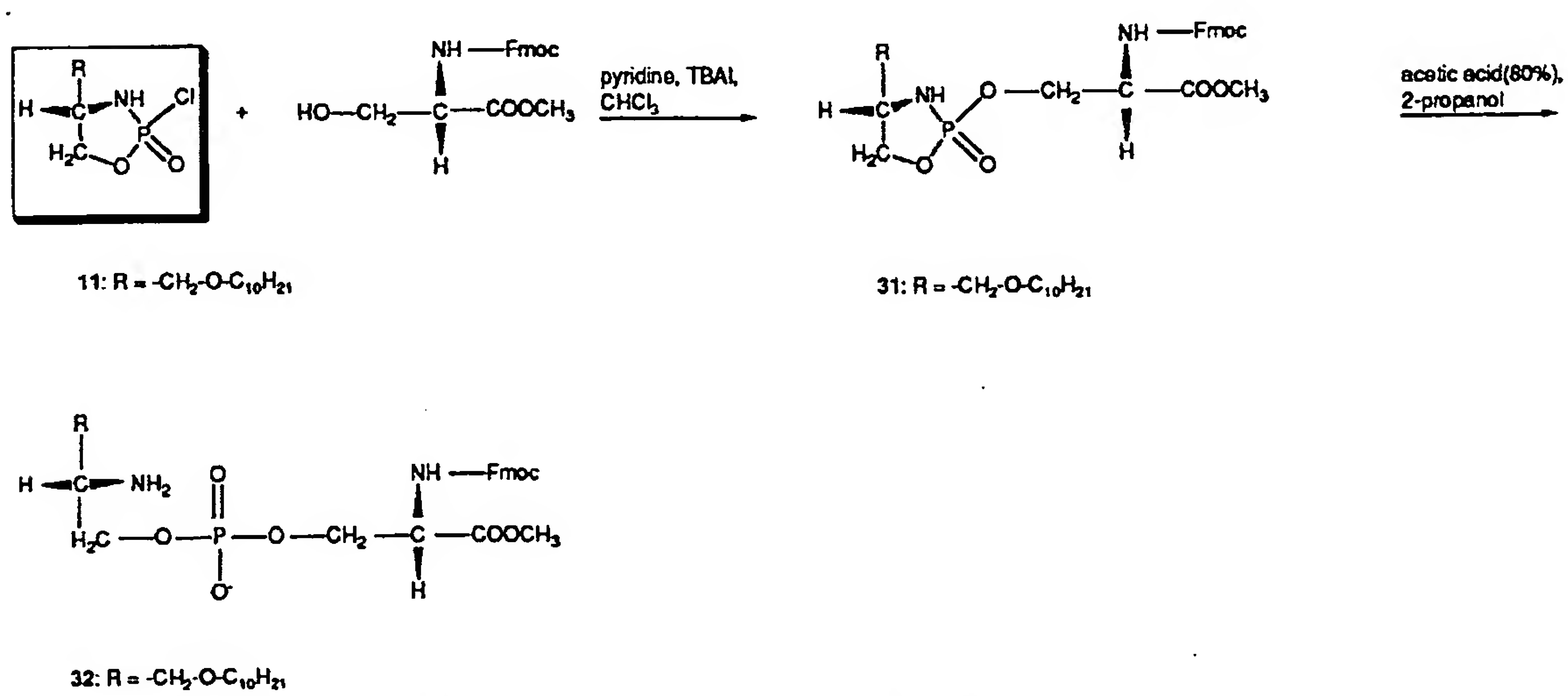

Fig. 3. Synthesis of 1-*O*-decyl-2-desoxy-2-amino-3-phospho-Fmoc-serine-methylester.

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in the presence of quinoline to give the 4-substituted-2-chloro-2-oxo-1-3-2-oxazaphospholanes (7)–(11) as intermediates (Scheme 1). These compounds could then be converted to different 2-amino-phospholipids: substitution of the remaining chlorine by nucleophiles lead to the 2′-substituted oxazaphospholanes (12)–(16) which could be hydrolyzed by 2-propanol/acetic acid under mild conditions. In order to obtain the 2-amino-3-phosphocholine for example, the choline function was introduced by nucleophilic displacement of the chlorine in compounds (7)–(11) with choline tosylate in the presence of TBAI. Acidic hydrolysis of the intermediates (12)–(16) finally lead to the desired 2-desoxy-2-aminolysophosphocholines (17)–(21) in 68% ((17), (18)) and 81% ((19)–(21)) yield (Fig. 1). The lower yield of the 2-amino-2-desoxy-glycerinic-acid derivatives (17) and (18) can be explained by partial ester hydrolysis accompanying the acidic cleavage of the respective oxazaphospholanes.

By the proposed method it was possible to obtain directly the desired 2-amino-2-desoxy-*sn*-glycero-phosphocholines in good yield, rendering protection and deprotection of the 2-amino group with trifluoracetanhydride, as reported by N.S. Chandrakumar and J. Hajdu [6], unnecessary. Moreover, desacetylation by anhydrous hydrochloric acid in methanol could not be applied to glycerinic-acid-esters, since the respective methylesters were formed under these conditions.

To test the scope and versatility of our route to the synthesis of other 2-amino phospholipid derivatives bearing different phosphatidyl head groups, we used 2-bromoethane-1-ol for substitution of the chlorine in the oxazaphospholane (11). This intermediate should, after hydrolysis of the substituted intermediate (27), lead to the 2-amino-3-phospo-ethyl-2′-bromide (28), a versatile precursor for 2-amino-3-phospho derivatives, allowing the introduction of various substituents at the 3-phospho-ethyl-2′-bromide moiety. Indeed, the sequence outlined above yielded the desired 2-amino analog (28) in 89% in the same way described above for the phospocholine analog (26). Subsequent exchange of the 2′-bromine with dimethylamine then afforded the 3-phospho-*N,N′*-dimethylethanolamine product (29) in 74% yield (referring to the aminoalcohol (1) as starting material) (Fig. 2).

Our synthetic scheme could also be extended to the preparation of 2-amino-3-phospho-serine derivatives: substitution of the chlorine in the oxazaphospholane (11) by Fmoc-L-serine-methylester in the presence of TBAI and subsequent hydrolysis of the intermediate (31) gave the 1-*O*-octyl-2-desoxy-2-amino-3-phospho-Fmoc-serine-methylester (32) in 81% yield (Fig. 3).

One-step preparation of 2-aza analogs of glycerinic acids ((17), (18)) opens a route to the preparation of 2-desoxy-2-amino-3-phosphocholine-glycerinic-acid-alkylesters ((22), (23)) in four steps, including two steps which require workup.

In conclusion our procedure describes a highly improved synthetic approach for the preparation of 2-amino-lysophospholipids with a reduced number of synthetic steps. The 2-chloro-2-oxo-1-3-2-oxazaphospholanes provide an intramolecular protection of the 2-amino group and present one single common versatile intermediate for the synthesis of different 2-amino-lysophospholipids bearing various phosphatidyl moieties. Thus our method appears to be of general value for the preparation of this class of compounds.

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